Biosimilars: what clinicians should know

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Biosimilar medicinal products (biosimilars) have become a reality in the European Union and will soon be available in the United States. Despite an established legal pathway for biosimilars in the European Union since 2005 and increasing and detailed regulatory guidance on data requirements for their development and licensing, many clinicians, particularly oncologists, are reluctant to consider biosimilars as a treatment option for their patients. Major concerns voiced about biosimilars relate to their pharmaceutical quality, safety (especially immunogenicity), efficacy (particularly in extrapolated indications), and interchangeability with the originator product. In this article, the members and experts of the Working Party on Similar Biologic Medicinal Products of the European Medicines Agency (EMA) address these issues. A clear understanding of the scientific principles of the biosimilar concept and access to unbiased information on licensed biosimilars are important for physicians to make informed and appropriate treatment choices for their patients. This will become even more important with the advent of biosimilar monoclonal antibodies. The issues also highlight the need for improved communication between physicians, learned societies, and regulators. (*Blood*. 2012;120(26):5111-5117)

Introduction

A similar biologic medicinal product, commonly referred to as biosimilar, is a copy version of an approved original biologic medicine whose data protection has expired. Since the implementation of a biosimilar approval pathway in 2005, several biosimilars, including somatropins, filgrastims, and epoetins, have been licensed and become available in the European Union (EU), and numerous other biosimilars, most importantly monoclonal antibodies, are being developed.[1] Recently, a biosimilar infliximab has been filed for regulatory review to the European Medicines Agency (EMA).[2] Product-class specific guidelines for these and other biologicals describing a targeted nonclinical and clinical development program are in place or currently under development.[3] In the United States, after the recent enactment of a specific approval pathway for biosimilars[4] and publication of the first draft guidelines on biosimilar product development by the United States FDA,[5] biosimilars are expected to be available soon. An EMA-FDA Biosimilar Cluster has been established for scientific discussion between the FDA and EMA and facilitation of global development of biosimilars. However, uptake of biosimilars in the European market has been slower than expected, which may, at least partly, be attributed to a lack of trust in the efficacy and safety of biosimilars as well as their interchangeability with the originator product by both patients and clinicians.[6]

This article addresses frequent concerns raised about biosimilars in the medical community and explains the scientific principles underlying the biosimilar concept established in the EU and put forward in the United States, allowing the licensing of biosimilars based on a reduced, or better scientifically tailored data package, which relies, as appropriate, on the extensive knowledge gained with the originator product.

What is special about biosimilars?

In principle, biosimilars are the biologic medicines' equivalent of chemical generics. However, biologicals are derived from living cells or organisms and consist of relatively large and often highly complex molecular entities that may be difficult to fully characterize. Because of inherent variability of the biologic system and the manufacturing process, any resulting biological will display a certain degree of variability (microheterogeneity), even between different batches of the same product. Because of unavoidable differences in the manufacturing processes, a biosimilar and the respective originator product, the reference product, will not be entirely identical. However, the amino acid sequence is expected to be the same, and only small differences in the microheterogeneity pattern of the molecule may be acceptable. A very thorough comparison of the structural and functional characteristics, and the product and process-related impurities of the biosimilar and the reference product will be necessary. Any differences found will need to be explained and justified with regard to the potential impact on the clinical performance of the biosimilar.[5,7]

Data requirements for the development and licensing of biosimilars are considerably greater than for small chemically synthesized

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and easily characterizable generic products. For a generic, physicochemical identification and demonstration of a similar pharmacokinetic profile (bioequivalence) to the originator product are usually sufficient to conclude on therapeutic equivalence. In contrast, a biosimilar needs to be developed based on a more extensive head-to-head comparison with the reference product, to ensure close resemblance in physicochemical and biologic characteristics, safety, and efficacy.[3,5] It should be emphasized that the scientific principles underlying the comparability exercise for biosimilars are the same as those for changes in the manufacturing process of a given biological, for which guidance and experience already exist.[8] However, because the biosimilar will be produced by a different manufacturer, the data requirements for demonstration of biosimilarity will usually be more extensive than for demonstration of comparability of a given biological before and after manufacturing changes by the same manufacturer.

As with generics, biosimilars are intended to be used at the same dose(s) and dosing regimen(s) to treat the same disease(s) as their reference products. Therefore, the focus of biosimilar development is not to establish patient benefit per se—this has already been done for the originator product—but to convincingly demonstrate high similarity to the reference product as basis for relying, in part, on its efficacy and safety experience. For these reasons, the study design, study population, and/or end points used in studies comparing the biosimilar with the reference product may be different from those previously used to establish therapeutic benefit of the reference product.

The type and extent of clinical data requirements for biosimilars vary and depend on the complexity of the active substance and how well it can be characterized, on the availability of an accepted surrogate end point to compare efficacy, on the type and seriousness of safety concerns that have been encountered with the reference product or the substance class, and on the possibility to extrapolate efficacy and safety data to other indications of the reference product, which have not been studied for the biosimilar. However, a repetition of the entire development program of the reference product is scientifically not necessary and could even be considered unethical.

Frequent concerns about biosimilars

Frequent concerns about biosimilars voiced by clinicians, mainly through learned societies, relate to their pharmaceutical quality, safety, and their interchangeability with the reference product. They also include doubts about clinical efficacy and safety in extrapolated indications for which no formal clinical studies have been performed with the biosimilar. Inconsistent terminology may also add to misperceptions about biosimilars.[9] It is thus necessary to discuss these concerns in view of the scientific principles established for biosimilars in the EU and shared in other highly regulated regions of the world:

1. The fear of low quality or substandard biosimilar products is not substantiated because the manufacturing process for a biosimilar must comply with quality requirements just as for any new biological and thus must demonstrate that the production process is capable of consistently producing a high-quality product. The manufacturing process needs to include state-of-the-art scientific knowledge and process understanding, which in some aspects may have evolved since the development of the originator product.[5,7] The extensive comparison of physicochemical and functional characteristics of the biosimilar with the reference product is an additional requirement and the foundation of biosimilar development. A recently published analysis supports the high pharmaceutical quality of biosimilars licensed in the EU.[10]

2. In our experience, the "similar but not identical" paradigm of biosimilars appears to fuel uncertainties about them. However, this principle is not new to biotechnology; even consecutive batches of originator products are never identical to each other—this is normal and is why adequate controls on batch to batch consistency have to be imposed. Indeed, biosimilars are usually specifically engineered and designed to closely resemble the originator molecule to the best extent possible using current technologies. Small differences (eg, in epitope or binding characteristics of a biosimilar monoclonal antibody) may have an impact on efficacy, but these would normally be picked up early on in product development from the extensive physicochemical and functional characterization required for biosimilars and biologicals in general. Sensitive state-of-the-art methods and methods orthogonally complementing these are very sensitive when used in combination. As mentioned in the section "What is special about biosimilars?", structural differences between a biosimilar and its reference product are only acceptable within the heterogeneity pattern of the molecule, and any differences found will need to be explained and justified with regard to the potential impact on the clinical performance of the biosimilar. One example of a difference, which has been accepted by EMA, is the increased level of phosphorylated high mannose-type structures in a biosimilar epoetin alfa compared with the reference product because the applicant could prove that these are common glycoforms of recombinant erythropoietins and cytokines and a large variety of nonlysosomal proteins from human plasma.[11]

3. Concerns have been expressed that the safety database of biosimilars could be insufficient at the time of approval, with immunogenicity being a particular concern.[12-19]

For a biosimilar, an extensive comparability exercise with the reference product is required, including human efficacy and safety data. Based on similarity being demonstrated with the reference product, the biosimilar can also refer to the safety experience gained with the reference product. Particularly for adverse drug reactions (ADRs) that are related to exaggerated pharmacologic effects, the demonstration of similar physicochemical characteristics, biologic activity, pharmacokinetics, and efficacy will already provide reasonable reassurance that such events can be expected at similar frequencies for the biosimilar and the reference product. The risk for detection of new (serious) adverse effects after licensing is considered much lower for a biosimilar than for a biological containing a new or modified active substance.

Immunogenicity, on the other hand, is an ongoing concern, especially for biologicals for which immune responses have been linked to serious safety issues, the most quoted example being pure red cell aplasia caused by cross-reacting neutralizing antibodies against erythropoietin. Immunogenicity may be influenced by patient-, disease-, or product-related factors. Patient- and disease-related factors are already known from the experience gained with the originator product and therefore do not need to be reinvestigated for the biosimilar. The focus of the evaluation is thus on potential product-related factors, such as structural alterations (eg, aggregation, which has been implicated in the immunogenicity of epoetins[20]) or impurities/contaminants, most of which are readily detected by state-of-the-art analytical methods. However, even seemingly small differences may have an impact on immunogenicity, and analytical or animal data cannot predict immune responses

in humans. Therefore, human immunogenicity data are generally necessary before licensing to exclude a marked increase in immunogenicity of the biosimilar compared with the reference product.[3,5,21] If the incidence of the immune response is known to be rare and thus unlikely to be captured before licensing, an additional post-marketing study designed to detect more subtle differences in immunogenicity may be requested, which, as in the case of biosimilar epoetins, can be of substantial size.

The current prelicensing requirements are supported by the finding of excessive immunogenicity for a biosimilar somatropin because of the presence of increased amounts of host-cell-protein, which could be eliminated by introduction of an additional purification step[22] and, more recently, the observation of 2 cases of neutralizing anti-epoetin antibodies associated with the subcutaneous use of a biosimilar epoetin alfa in a clinical trial in patients with renal anaemia, resulting in premature study termination.[23] A thorough root-cause analysis of the latter cases identified tungsten-mediated unfolding and aggregation of the epoetin alfa as a potential cause for the increased immunogenicity.[20] Because the soluble tungsten found in some of the syringes used for the product is not present in the drug product per se but stems from the manufacture of the syringes, this problem, if confirmed, could also be relevant to other epoetin-containing products. It should be emphasized that immunogenicity is a potential concern for all biologicals, not just for biosimilars.

4. The need for strict postmarketing surveillance and potentially large, post-marketing studies for complete reassurance regarding the safety of biosimilars, particularly epoetins, has been highlighted.[6,18] For a biosimilar, as for any new drug, a comprehensive risk management plan, including a plan for post-authorization safety surveillance, has to be submitted to the authorities at the time of the marketing authorization application.[24] This must address identified and potential safety concerns for the biosimilar, the reference product and/or the substance class. The post-marketing program for a specific drug product is tailored taking into account these considerations and to best evaluate potential remaining risks. Thus, the safety of biosimilars is actively and comprehensively followed up on an ongoing basis.

5. The basis for considering the efficacy of a biosimilar to be comparable to that of the reference product has been questioned.[6] Specifically, the acceptance range for therapeutic equivalence for biosimilar epoetins was considered wide.

As stated in the section "What is special about biosimilars?" above, the intention of the biosimilar development is to show similarity with the reference product, not to independently demonstrate patient benefit. Therefore, the study population should be as homogeneous as possible, reasonably sensitive to the effects of the biological and the end points should ideally reflect its unconfounded pharmacologic action to create a sensitive test model. This should be able to detect potential drug-related differences in efficacy and safety and to minimize variability caused by disease- or patient-related factors. End points measuring activity of the drug are usually more sensitive for detecting product-related differences than hard end points evaluating patient benefit and may be acceptable if they are clearly related to the desired clinical effects. Examples of pharmacodynamic parameters that have been accepted as surrogate end points for the evaluation of efficacy of biosimilars in the EU include glucose infusion rate in clamp studies for insulins, absolute neutrophil count for G-CSF, and number of oocytes retrieved (in the context of in vitro fertilization) for follicle-stimulating hormones.[3] On the other hand, efficacy of a biosimilar somatropin still has to be assessed in a clinical trial of at least 6 months' duration in growth hormone-deficient children because insulin-like growth factor 1, although a good marker of pharmacologic activity of a somatropin, lacks clear relationship with growth response.

In a statistical and regulatory sense, therapeutic equivalence infers that the test drug does not have better or worse efficacy than the reference product, thus allowing the use of the same dosage for the same indication, as is intended for biosimilars. When defining comparability margins, clinical considerations need to be taken into account; the selected margins should represent the largest difference in efficacy that would not matter in clinical practice. Treatment differences within these margins would thus be acceptable because they have no clinical relevance. The principles of margin selection are not unique to biosimilar testing but are used in any clinical trial comparing treatment alternatives or prechange and postchange product in case a biological has undergone a change in its manufacturing process and clinical data are required for assessment of comparability. Comparability margins proposed for licensing studies for a given medicinal product, including biosimilars, will always need sound scientific justification to be acceptable for regulators.

The acceptance range of $\pm$ 0.5 g/dL in blood hemoglobin concentrations for demonstration of similar efficacy of a biosimilar and the originator epoetin as suggested in the respective EMA guideline is considered tight in the view of the rather high background variability in blood hemoglobin levels in patients with renal anemia, especially those on dialysis.[3] It should be noted that, not only the observed mean treatment difference (between biosimilar and reference product) but also the 95% confidence interval of this difference needs to be fully contained within the equivalence margins, thus providing sufficient statistical reassurance that efficacy is indeed similar. The assumption that patients switched from an originator product to the respective biosimilar may need to change dosage, dosage intervals, or route of administration is unsubstantiated.[25]

6. Concerns have been expressed about using biosimilars in indications or in patient populations that are approved for the reference product but have not been formally investigated during the clinical development of the biosimilar and, therefore, have been licensed on the basis of extrapolation of efficacy and safety data.[6,12,17,19,25-28] In this respect, particular concerns have been raised regarding the use of biosimilar G-CSF for the mobilization of stem cells in healthy donors and the use of biosimilar epoetins in patients with cancer.[25,29,30] In addition, there is growing concern in the rheumatology, gastroenterology, and dermatology communities regarding the future use of biosimilar anti-inflammatory monoclonal antibodies based on extrapolation of data.[31-33]

It must be clearly understood that a biosimilar, as opposed to a small chemical generic, cannot automatically claim all indications of the reference product and that any extrapolation of data requires sound scientific justification.[34] For extrapolation of data to be considered, several requirements need to be fulfilled:

A. Similarity with the reference product must be convincingly demonstrated, based on the totality of the evidence from a thorough comparability exercise. Clinicians need to be aware that clinical data are not the only cornerstone of a biosimilar development to be relied on. Extensive characterization and comparison of the physicochemical properties and biologic activity of the biosimilar and the originator product play a fundamental role in this, and close

similarity in these aspects is a prerequisite for any reduction in the amount of nonclinical and clinical data requirements. Clinical data provide complementary information (eg, regarding the clinical relevance of any observed differences and on immunogenicity).

B. If clinical similarity can be shown in a key indication, extrapolation of efficacy and safety data to other indication(s) of the reference product may be possible (eg, if the relevant mechanism of action and/or the receptor(s) involved in the extrapolated indications are the same).[3] If the mechanism of action is different or unknown, additional convincing data [eg, on pharmacodynamic parameters and/or specific and sensitive functional assays reflecting the respective pharmacologic action(s)] are necessary to provide further reassurance that the biosimilar will behave as the originator product in these indications. In this sense, comparative pharmacodynamic studies in healthy subjects are required for biosimilar G-CSF, evaluating, in addition to absolute neutrophil count, the $CD34^+$ cell count to assess mobilization of stem cells from the bone marrow.[3] Such data should not be considered in isolation but as a further building block in the overall proof of biosimilarity. Based on such considerations, extrapolation of efficacy and safety data to other indications of the reference product has been approved for biosimilar somatropin, epoetin, and filgrastim-containing medicinal products.[1]

C. Another prerequisite for extrapolation is that the safety profile of the biosimilar must have been properly characterized and unacceptable immunogenicity excluded. Extrapolation of immunogenicity data is only possible from high-risk to low-risk patient populations and clinical settings. For example, pure red cell aplasia resulting from neutralizing anti-epoetin antibodies is a potential concern for subcutaneous use of epoetins in patients with renal anemia but less for intravenous administration or use in cancer patients receiving chemotherapy. Therefore, extrapolation of immunogenicity data is considered possible from subcutaneous use in renal anemia patients to intravenous use in the same population or to subcutaneous use in immunocompromised cancer patients but not vice versa. In this respect, the concern expressed in a recent review,[35] that immunogenicity data collected for intravenous use of epoetin could be extrapolated to subcutaneous use, is not substantiated because the respective guideline[3] clearly states that comparative immunogenicity data will always be required for subcutaneous use, if applied for.

In this context, it should be emphasized that the scientific principles of extrapolation of data are not new for biosimilars but also apply to the comparison of prechange and postchange product on a change in the manufacturing process of a biological, which is already licensed for use in several indications. To the knowledge of the authors, up to now, there has not been a case, even with extensive changes to the manufacturing process, where new clinical data have been generated or requested in every indication because the overall data from the comparability exercise already conclusively demonstrated that the manufacturing change has no adverse impact on efficacy and safety.

In conclusion, extrapolation of data to other indications of the reference product, and thus formal lack of a clinical trial in the respective clinical indication, does not imply less reassurance as regards efficacy and safety of the biosimilar if all the aforementioned considerations are taken into account, and represents a logical consequence of the scientific concept. Therefore, clinicians should have confidence in using biosimilars for all indications for which they have been licensed.

7. The question has been raised whether biosimilars could be considered interchangeable (in the sense of a therapeutic alternative initiated by, and under surveillance of the treating physician) with the respective reference product and, consequently, the concern that automatic substitution at the pharmacy level (without the knowledge of the physician) might follow.[6,18,28]

Undoubtedly, biosimilars developed in line with EU requirements can be considered therapeutic alternatives to their respective reference products. Interestingly, it has been stated that the originator products epoetin alfa and epoetin β are considered as interchangeable by healthcare professionals because of the long medical experience with both products.[36] Although both epoetins can undoubtedly be considered efficacious and safe, similarity has never been demonstrated in a head-to-head comparison and dosage recommendations are not fully identical as would be required for a biosimilar.

The main argument against automatic substitution is the concern regarding traceability, which is necessary for a root cause analysis in case an ADR occurs.[6,17,30,35] The importance of reliable traceability of biologicals has been acknowledged, particularly for epoetins, and a respective statement has been introduced into the prescribing information of all epoetins licensed in the EU.[37] In addition, the novel pharmaceutical pharmacovigilance legislation being implemented in 2012 should, among other things, ensure European-wide traceability of medicinal products.[38] Another, more theoretical concern regarding automatic substitution is the possibility that repeated switches between the biosimilar and the reference product may increase immunogenicity with potentially negative effects on the safety and/or efficacy of the products.[13,36] This would, however, also apply to switches between different originator biologicals of the same class. Automatic substitution may be difficult from a practical viewpoint, especially for patients self-administering the medicinal product, in case of differences in injection devices, preparation and handling of the biosimilar, which may increase the risk of medication errors or impair treatment compliance.

It has been suggested that a change from an established epoetin to a biosimilar agent should require informed consent from the patient.[39] Although the authors agree that patients should always be informed about the medicine they are prescribed or given, the necessity of an informed consent for the switch to a biosimilar is considered a disproportionate measure because biosimilars, as any new drugs, are scrutinized by the competent authorities during the marketing authorization procedure to ensure that only products with adequate quality, efficacy, and safety are approved.

It should be noted that substitution policies are decisions outside the remit of the EMA because the regulation of substitution of medicinal products is the responsibility of the individual EU member states. To our knowledge, up to now, automatic substitution has not been implemented for any biosimilar in the EU; and, according to the European Generics Association, more than a dozen countries across Europe have introduced rules to prevent automatic substitution of biologic medicines by biosimilars.[40]

Implications for patients and treating physicians

The expected benefits of biosimilars are reductions in acquisition expenses and consequently better access to biotherapeutics while

containing health expenditure.[41] Because of the long development time and related high costs of biosimilars, partly because of considerable regulatory requirements to ensure their quality, safety, and efficacy, the reduction in their acquisition price is unlikely to be as profound as for chemical generics. Still, the absolute price difference between biosimilar and originator products can be substantial for expensive biopharmaceuticals and can be expected to increase as biosimilars gain market share. For instance, it has been estimated that a 20% price reduction of 5 off-patent biopharmaceuticals would save the EU > €1.6 billion per year and the US federal government $9 billion to $12 billion over the next 10 years.[41,42]

Of course, physicians should only prescribe medicines for which quality, safety, and efficacy have been demonstrated according to state-of-the-art science and technology, with the exception of drugs used in clinical trials or for compassionate purposes. Because biosimilars are licensed based on a reduced data package, physicians might misinterpret this as a nonreassuring basis to use biosimilar drugs for their patients. To alleviate unsubstantiated fears, physicians need to gain a clear understanding of the biosimilar philosophy, including the scientific principles as discussed in this article. The data package required for licensing of a biosimilar is not simply reduced. It is scientifically tailored and includes an extensive comparability exercise using sensitive analytical tools and sensitive test models to provide reassurance that the biosimilar and the respective reference product are indeed highly similar. Based on such extensive comparative data, there is no scientific reason to assume that the biosimilar would behave differently from the reference product when used in clinical practice.

The understanding of the biosimilar concept will become increasingly important when even more complex biologicals, such as monoclonal antibodies, are developed as biosimilars.[43] For example, the most sensitive clinical model for investigating potential product-related differences in efficacy of anticancer monoclonal antibodies might not necessarily use overall survival as the primary end point, which is usually considered as the gold standard to establish patient benefit. However, overall survival is usually confounded by many factors unrelated to the performance of the drug itself, which might, despite randomization, not be sufficiently balanced between treatment groups unless the study is extremely large. For a biosimilar, other primary clinical end points that are more sensitive (eg, objective response rate or change in tumor mass), focusing on the detection of potential differences in efficacy rather than the demonstration of efficacy per se, may be more appropriate.[44]

With regard to safety, physicians should understand that the nonidentical nature of a biosimilar and the more familiar reference product is inherent to all biologicals, and is also true for differences that might arise from a change in the manufacturing process of an established biologic product.[45] It is well known that the problem of epoetin antibody-induced pure red cell aplasia was first recognized after a major change in the manufacturing process used for an originator epoetin, and not with a biosimilar.[46] Because immunogenicity may be altered by such major but also by seemingly minor changes, human immunogenicity data are always required for the licensing of biologicals, including biosimilars.

Regulatory oversight and scrutiny are important to ensure the safe use of any biological. In particular, active postauthorization surveillance is a key factor. Therefore, physicians would be well advised to always document exactly which biological is used for an individual patient, as has been established for plasma-derived medicinal products. If an ADR occurs or is suspected, it is important to identify the specific product causing it. Thus, ADR reports should include, in addition to the International Nonproprietary Name, other indicators, such as brand name, manufacturer's name, lot number, and country of origin of the batch used.[47] This highlights the central role of well-informed and vigilant prescribing physicians and pharmacists in the overall concept of regulatory control of patients' health.

Finally, clear information about existing guidelines, access to unbiased information on biosimilars, and education of physicians regarding the clinical utility of biosimilars as well as improved communication between learned societies and regulators have been requested.[18,19,48]

Guidelines on the requirements for the development and licensing of biosimilars and responses to comments received during the external consultation phase are posted on the EMA homepage.[3] Information on the documentation submitted in support of a specific biosimilar application and the related scientific discussion and considerations of the Committee for Medicinal Products for Human Use are also publicly available as European Public Assessment Reports.[1] In addition, the prescribing information of a biosimilar product provides information about its biosimilar nature and directs the reader to the EMA homepage for further detailed information, which may assist physicians in making informed and appropriate treatment choices for their patients. The Working Party on Similar Biological (Biosimilar) Medicinal Products (BMWP) is open to discussions with all stakeholders and welcomes scientific input on their guidelines. Considering the previous absence of feedback from the European medical associations on the biosimilar guidelines, BMWP considers a more proactive approach to better involve the organized medical community in the public process of creating and updating the guidelines. To reassure practicing physicians, quality, safety, and efficacy of biosimilars are a key priority and of paramount importance to the BMWP in its efforts to act in the best interest of patients and particularly to ensure patient safety.[18]

Summary of key points

• The principles guiding biosimilar development are scientifically sound and shared in the European Union, the United States, and other highly regulated regions of the world.

• The scientific principles for establishing biosimilarity are the same as those for demonstrating comparability after a change in the manufacturing process of an already licensed biological.

• A biosimilar should be highly similar to the reference product in terms of physicochemical and functional characteristics, and clinical performance.

• The focus of biosimilar development is not to establish patient benefit per se but to convincingly demonstrate close similarity to the originator product as a basis for relying, in part, on efficacy and safety experience gained with this reference product.

• The biosimilar development program is scientifically tailored using up-to-date analytical tools and sensitive test models to best detect even small potential product-related differences between the biosimilar and the reference product. Clinical end points may thus be different from those used in the reference product's clinical trials if clinically meaningful and scientifically justified.

• Extensive structural and functional characterization and comparison of the biosimilar and the reference product are the foundation of biosimilar development.

• The primary amino acid sequence should be the same for the biosimilar and the reference product. Small differences in the

micro-heterogeneity pattern of the molecule may be acceptable if appropriately justified with regard to its potential impact on safety and efficacy.

• The requirements for the pharmaceutical quality of biosimilars are the same as for any new biological.

• The type and magnitude of clinical data requirements depend on the complexity of the active substance and how well it can be characterized, on the availability of an accepted surrogate end point to assess efficacy, on the type and seriousness of safety concerns, and the possibility to extrapolate efficacy and safety data to other indications of the reference product.

• Human safety (including immunogenicity) data are always required for biosimilars before approval.

• Extrapolation of efficacy and safety data to other indications of the reference product that have not been investigated during the clinical development of the biosimilar always requires convincing scientific justification, which should address the mechanism of action, toxicities, and immunogenicity in each indication of use.

• Decision-making of the regulatory authority is based on the totality of the evidence provided by the applicant in support of biosimilarity.

• A risk management plan for post-licensing surveillance is routinely required for all new drugs, including biosimilars.

• Traceability is important for all biologicals, including biosimilars.

• Biosimilars can be considered therapeutic alternatives to the reference product.

• Information on licensed biosimilars is available from the European Public Assessment Reports and may further assist clinicians in making informed and appropriate treatment choices for their patients.

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